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Calcium and Metabolic Bone Disorders

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Abstract

Calcium homeostasis has a pivotal role in regulating many biological processes. The interplay of calcium-regulating hormones, including parathyroid hormone (PTH), vitamin D, and calcitonin, is crucial in tightly maintaining serum calcium levels. Deregulation of calcium homeostasis has clinical implications resulting in hypercalcemia or hypocalcemia, which can lead to metabolic bone disease (MBD). MBD is a group of multifactorial bone diseases, caused by bone demineralization and characterized by an increased susceptibility to fracture risk. This chapter aims to provide an overview of associated risk factors and diagnostic, prevention, and recent treatment methods for MBD. The diagnosis of MBD is based on the assessment of clinical signs, radiological findings, quantitative ultrasonography, and biochemical evaluation of serum calcium, phosphate, PTH, alkaline phosphatase, and vitamin D. Current pharmacological treatments include antiresorptive and anabolic conventional therapies. Additionally, the efficacy of herbal extracts and nutritional supplements have been evaluated. Recent advances in the MBD management include drugs targeting calcium-sensing receptor and parathyroid hormone-related proteins, leading to the development of cathepsin K and Src tyrosine kinase inhibitors, calcilytics, and monoclonal antibodies against sclerostin or Dickkopf-1. Moreover, new nanomaterials have been used for improving the surgical treatment of vertebral fractures.

Keywords: calcium, parathyroid hormone, metabolic bone disease, osteoporosis, vitamin D, anabolic drug, antiresorptive drugs

1. Introduction

Metabolic bone disease (MBD), the third most prevalent disorder of the endocrine system, involves any disorder that alters the phenomena of mineralization in the normal skeleton. The disorder is primarily caused by abnormalities in the structure of bone or its mass, vitamin D level as well as the presence of certain minerals such as calcium and phosphorus [1].

The concentration of extracellular calcium is crucial for several functions at the cellular level, which needs to be retained in restricted levels. The free concentration of calcium is predominantly negatively regulated by the secretion of the parathyroid hormone (PTH) in response to calcium-sensing receptors. A substantial drop in the level of free calcium activates the release and synthesis of PTH, which often leads to calcium reabsorption in the renal tubules, enhanced secretion of calcitriol (vitamin D₃)

promoting calcium absorption from the intestine, and immediate release of calcium from the skeleton, which contains 99% of calcium in the body. Conversely, in regard to rising levels of calcium in the body, PTH level drops that lead to a decline in the above-stated processes. This balance is seen to be disturbed in various pathological circumstances leading to elevated or low calcium levels. High calcium levels, known as hypercalcemia, and low calcium levels, known as hypocalcemia, are observed in conditions such as hypoparathyroidism and vitamin D deficiency.

The most common forms of MBD comprises of osteoporosis, osteomalacia, primary hyperparathyroidism, and fluorosis, while fibrous dysplasia, Paget's disease, osteogenesis imperfecta, and tumor-induced osteomalacia account for its rare forms.

Osteoporosis is a severe MBD that constitutes to be a serious health issue for older people. It represents a decline in the bone mass per unit volume, leading to significant weaknesses in the bone structure, which ultimately leads to bone deformity/fracture. Osteoporosis is categorized as primary when there is no prominent diagnosis of the disease and secondary when an established contributing cause such as steroid treatment is detectable. Type I (postmenopausal) and type II (age-related) are categorized under primary osteoporosis. Type I osteoporosis incorporates bone loss with the expedited bone mass reduction due to the withdrawal of estrogens [2].

Osteomalacia results from curtailed absorption of calcium and phosphate in the intestine due to a deficiency in vitamin D or more rarely due to calcium or phosphate deficiency. Joint pain with fragility in bone and muscular weakness are the common symptoms observed in patients with osteomalacia [3].

Paget's disease leads to skeletal lesions resulting in progressive bone turnover. The finely constructed bone lacks a natural lamellar framework and has poor quality with effects like bone deformity with prominent fractures and related pain [4].

Hyperparathyroidism results due to excess secretion of PTH, which can be categorized as primary hyperparathyroidism or secondary hyperparathyroidism. Primary hyperparathyroidism occurs due to the raised concentration of calcium in the serum. Research reports show hypercalcemia with an abnormally high level of alkaline phosphatase and elevated serum PTH [5].

Fibrous dysplasia is categorized as a rare form of metabolic disorder in which the bones are covered with irregular structures, which appear as a scar-like fibrous tissue. This deposited structure affects bone structure and integrity, making it more fragile and fracture-prone.

This chapter discusses in brief about the associated risk factors and diagnosis of MBD along with the preventive measures and the pharmacological approaches for the treatment of MBD.

2. Associated risk factors

Several contributing factors that control bone mass are diet, lifestyle, levels of cytokines, level of mobilization and physical activity, hormones, genetic factors, and local growth factors. **Table 1** illustrates premature risk factors associated with MBD for both antenatal and postnatal period.

The amalgamation of various nutritional and biomechanical factors results in the precipitation of MBD. Some of them are discussed below:

2.1 Vitamin D deficiency

Vitamin D is inevitable for retaining the rate of metabolism in bone. The major function of vitamin D is to boost calcium and phosphorus intestinal absorption by its

Antenatal	Postnatal
Preclampsia	Liver and kidney disease
Placental insufficiency	Use of drugs such as loop diuretics, methylxanthines, glucocorticoids
Prevalence of neuromuscular disorders, intraventricular hemorrhage	Prevalence of bronchopulmonary dysplasia

Table 1.
List of premature risk factors associated with metabolic bone disorders for both antenatal and postnatal period.

active metabolite 1,25dihydroxyvitamin D3 along with fostering the continuance of neuromuscular function as well as bone remodeling. Disorders in which this active metabolite is deficient can pose a greater risk of the incidence of bone disorders [6]. Low levels of vitamin D results in decreased absorption of intestinal calcium and phosphorus, with a drop in the level of calcium in serum with an increased synthesis of PTH. A rise in the level of PTH in plasma preserves the level of normal serum calcium by enhancing 1,25-(OH)₂D renal development, growing bone yield, and escalating loss in mass of bone. Lack of sufficient intake or a maternal lack of vitamin D is the most leading cause of deficiency of vitamin D. Renal failure or the incidences of hepatic disease, receptor defects, or synthesis of congenital vitamin D are the other instances that cause a vitamin D deficiency. Additionally, two other rare genetic diseases, including vitamin D-dependent rickets type 1 or pseudovitamin D deficiency rickets, are caused due to the mutation in the gene encoding 1 α -hydroxylase enzyme (CYP27B1 gene), which is a rate-limiting enzyme involved in the bioactivation of vitamin D.

A recent report has evaluated vitamin D status and its relationship with skeletal health in 40 healthy adult Nigerians (aged between 21 and 50 years) [7]. An array of physiological parameters were evaluated, which predominantly included markers of bone health, thyroid function and renal function, levels of parathyroid hormone, calcium excretion rates, and serum 25-hydroxyvitamin-D levels. The observed results indicated the fact that approximately 70% of the reported cases had an incidence of vitamin D insufficiency with 25% of the subjects indicated osteopenia, while none of the subjects presented with osteoporosis. The bone mineral density (BMD) T-score for osteopenic subjects was significantly lower than for non-osteopenic subjects. It was also observed that osteocalcin levels in serum were considerably higher in osteopenic subjects versus non-osteopenic subjects; however, a 24-hour calcium excretion was comparable between the two groups. Mean serum 25-hydroxyvitamin-D was lower in subjects with osteopenia compared to non-osteopenic subjects, while parameters for thyroid, renal, and calcium-phosphorus were not significantly different in the observed group [7].

2.2 Disorders related to homeostasis of calcium and phosphorus

Disorders related to homeostasis of calcium and phosphorus results in ultimate clinical consequences for neonates. A fine positive balance between calcium and phosphorus is indispensable for sufficient bone growth and maturation. Neonates with persistent malabsorption are at high prospects of poor absorption of calcium, phosphorus, magnesium, or vitamin D, either due to medical or surgical interventions [8].

2.3 Drug-related factors

Some drugs that are frequently used in premature births also support the incidence of MBD. Some of the prominent classes of such drugs are loop diuretics such

as furosemides, corticosteroids, methylxanthines, antifungals, and certain antiepileptics. The most probable reason may be activation of osteoclasts and reduction of osteoblast proliferation and decreased absorption, thereby the ultimate elimination of calcium by the kidneys [9].

2.4 Parent related nutrition

The concentration of minerals such as calcium and phosphorus in premature breast milk is inadequate in regard to the estimated requirement, presuming that they ingest approximately one third that is essential in fetal life [9]. In addition, milk products are high in concentration of the stated minerals but have a lower bioavailability; hence, consumption of mineral fortified milk is essential for preventing and treating MBD.

2.5 Biomechanical factors

Biomechanical factors that impact the alteration of bone structure is accountable for the reduction of bone mass caused by reduced activity level. The majority of bone-loading process occurs during the third trimester. Nevertheless, in the absence of bone loading, bone formation stops and further osteoclasts are activated leading to a reduction in bone strength [10]. Neonatal demineralization of the skeleton may result from immobilization due to the prevalence of other disease conditions or neurological implications.

2.6 Endocrinology-related factors

Thyroid hormones are prerequisite for the development of the skeleton and are prime regulators of bone maintenance. Hypothyroidism induces delayed development of the skeleton and growth retardation with delayed bone development owing to inadequate endochondral ossification. Hyperparathyroidism also impacts bone metabolism, which causes significant conditions such as hypercalcemia, demineralization of the bone, and delay in growth and development. Due to these abovementioned-stated issues, a decline in the normal function of kidneys eventually leads to mineral and bone metabolism disturbances culminating in serious skeletal deformities [11].

3. Diagnosis

Since there are no ultimate diagnosis and therapy indications for MBD, and the related sign and symptoms also appear very late, it is, therefore, appropriate to monitor the subjects at risk for the development of the related disorder.

3.1 Serum markers

Levels of alkaline phosphatase (ALP) rise physiologically at about 6–12 weeks of age over the first 3 weeks of life. Regardless of the lack of signs and symptoms, ALP levels > 500 IU/L suggest impaired bone homeostasis and values >700 IU/L is associated with bone demineralisation [12].

Serum phosphate levels <5.6 mg/dl are strongly linked with the prevalence of the radiologically apparent disorder in preterm infants with an average gestational age of 24.7–33.0 weeks [13].

3.2 Urinary markers

Hypophosphatemia is the most prevalent physiological modification coupled with premature MBD, which causes a reduced release of PTH and thereby increases the reabsorption of phosphate from the renal tubular. Infants born <28 weeks of gestation have a reduced baseline value for phosphate, resulting in increased excretion of phosphate in urine, even in the mere existence of lower levels of phosphate that appear as a significant marker for MBD incidence [14].

3.3 Radiological markers

Dual-energy X-ray absorptiometry (DEXA) is the conventional method used for BMD assessments. DEXA employs the use of low ionizing radiation and measures the calcium content in bone in terms of grams of hydroxyapatite/cm².

Quantitative ultrasound is another technique that is relatively inexpensive and measures the mineral content of bone as well as the organic matrix. The parameters that are evaluated by the abovementioned technique are the speed of sound and bone transmission time [15].

4. Prevention of MBD

There are certain non-pharmacological approaches that need to be inculcated in daily life for the prevention of MBD. Some of them are discussed below:

4.1 Physical activity

Individuals with MBD should be educated about the potential advantages of physical activity and motivated to be active within their ability and in keeping their values and goals as realistically possible. They should be given training on how to self-monitor for signs and symptoms that should be brought to their healthcare team's attention and the emergency contact information for this team should be issued [16].

4.2 Adequate calcium and vitamin D intake

The Institute of Medicine (IOM) prescribes that dietary calcium consumption should be limited to 1000 mg daily for men aged 50–70 years, and 1200 mg daily for women aged 51 years and over [17]. Presently, the impact of calcium supplementation on stone formation is unclear. Large doses of supplemental calcium are likely to lead to stone formation, especially if given separately from a meal. If appropriate, patients with stones should be advised to take a meal with calcium supplements, and further, the disease condition needs to be closely monitored [18].

Vitamin D is a vital component of calcium absorption, which helps in the maintenance of bone health. The IOM recommends 600 IU and 800 IU per day for men and women who are aged 51–70 years and over 70 years, respectively [17]. Earlier reports indicate the fact that combined vitamin D and calcium intake demonstrated a reduction in the risk of fracture in older adults, but the effects varied according to the study setting, i.e., institution versus community dwellers. The risk of fracture among older adults was lower in the community dwellers than for institutionalized elderly people. However, further research is required for appropriate dose and dosing regimens to end up in a conclusive remark [19].

4.3 Adequate protein intake

Maintaining an appropriate intake of proteins is vital for maintaining musculo-skeletal functioning in postmenopausal women and men over the age of 50 years. The recommended protein intake is 0.8 g/kg/day [20].

4.4 Reducing the intake of caffeine

The impact of various caffeinated beverages has been inferred as a trigger of osteoporosis and fragility fracture in individuals; hence, it is recommended to restrict the intake of caffeine [21].

5. Treatment approaches for MBD

The recent decade has witnessed much progress in the introduction of new medications for the treatment of MBD. The treatment modality of this group of disorders comprises two major treatment regimens, antiresorptive and anabolic conventional therapies. Antiresorptive drugs predominantly reduce the bone resorption rate, while anabolic drugs boost the formation of bone. The following medicines for skeletal disorders, including Paget's disease of the bone, osteoporosis, MBD, and several other rare type of bone diseases, form the basis of our current clinical treatment regimen.

5.1 Antiresorptive agents

The major class of drugs included in this category includes bisphosphonates, estrogens, calcitonin, and denosumab.

Bisphosphonates, first-line antiresorptive bone agents, are commonly used to treat osteoporosis caused by glucocorticoids and other disorders marked by severe osteoclastic bone resorption, such as humoral malignant hypercalcemia, Paget's disease, multiple myeloma, and osteolytic bone metastasis [22]. The drugs specifically included in this group for the treatment of MBD comprises of alendronate, risedronate, and zoledronic acid. Such groups of therapeutic agents bind with a high affinity to the bone's mineral matrix and prevent resorption of osteoclast of the bone, resulting in reduced bone turnover and a significant increase in bone mass [23]. The most prominent side effect related to bisphosphonates administered orally is the upper gastrointestinal discomfort, which majorly includes the erosion of the esophagus leading to ulcer, heartburn, and indigestion.

Calcitonin is approved for the treatment of osteoporosis care in postmenopausal women when alternative therapies are not practicable [24].

Denosumab, the first biological agent available for osteoporosis treatment, is a fully human monoclonal antibody that acts by inhibiting transmembrane protein (RANKL), which has proven results for the formation and functioning of osteoclasts, thereby reducing bone resorption. It is usually recommended for the patients who are unable to be on drug therapy, which are orally administered but are at high risk for the incidence of fractures. Denosumab is well-tolerated, but associated hypersensitivity or dermatological reactions, musculoskeletal pain, infections, and hypercholesterolemia are the major documented adverse effects. It can trigger hypocalcemia, so calcium levels should be fixed before starting treatment [25, 26].

5.2 Estrogen agonist/antagonist

Estrogen therapy is FDA approved exclusively for the prevention of osteoporosis in postmenopausal women who are at high risk, and should only be used

when non-estrogenic osteoporotic medications have been deemed inappropriate. Hormonal replacement therapy is no longer recommended as a first choice for treating and preventing osteoporosis in postmenopausal and premenopausal women due to the overall associated health risks that hugely outweigh the benefits.

While antiresorptive drugs usually display a lower incidence of associated side effects, bone turnover suppression can elucidate the necrosis of the jaw and the incidence of atypical femur fractures that can be documented in patients with long-term bisphosphonate usage [27]. Because antiresorptive agents are unable to preserve bone mass and bone integrity, it continues to be of core interest to identify molecular targets that would promote osteoblast activity and lead to enhanced bone mass with reconstructed skeletal architectures.

5.3 Anabolic conventional therapies

Osteoanabolics are another category of drugs, which covers the PTH and parathyroid hormone-related peptide analogs. PTH functions as an efficient endocrine regulator for the maintenance of calcium and phosphate concentrations in extracellular space, vital to the preservation of concentration of calcium in serum and urinary samples within the normal physiological limit. High PTH levels lead to a high bone-turning state with bone resorption exceeding bone formation and ultimately osteoporosis precipitation [28].

Teriparatide was the first anabolic treatment option approved for the treatment of osteoporosis, which has a mode of action similar to that of the PTH hormone. This works by triggering the development of new bone by increasing osteoblastic development when given in low doses [29]. In patients with Paget's bone disease, elevated concentrations of alkaline phosphatase, prior skeletal radiotherapy, recurrent or metastatic bone malignancy, hypercalcemic disorders such as primary hyperparathyroidism, avoidance of the treatment is suggested [30]. Abaloparatide is another FDA approved drug for the treatment of osteoporosis in postmenopausal women. It is further advised to avoid the treatment in patients with preexisting hypercalcemia and disorder such as primary hyperparathyroidism [31].

Another promising investigational drug is romosozumab, which is a sclerostin-neutralizing antibody. Reports have shown elsewhere that it is better alternative bisphosphonate alendronate in women with severe osteoporosis for reducing the risk of prominent clinical fractures. This was accompanied by a boost in bone formation markers with a decline in bone resorption markers, implying the action of both stimulating bone formation and inhibiting bone resorption [32].

Apart from these two major classes of drugs, various herbal medicines are also gaining attention for being used in the treatment of MBD. Some of them include Hachimi-jio-gan and Juzen-taiho-to, *Kami-kihi-to*, *Bushenningxin*, *Shu Di Shan Zha*, and so on, which have proven reported results in various animal models on improving bone health [33, 34]. Reports suggest the fact that Hachimi-jio-gan and Juzen-taiho-to significantly prevented the loss of bone in SAMP6, a murine model for senile osteoporosis [34]. The decoction containing Bushenningxin caused osteoblasts to have an increase in the number of cell organelles with clear Golgi apparatus, increased proliferation, and inhibition of apoptosis for a time period of 12 weeks when given to OVX mice [35].

Recent advances in MBD treatment include medications that target calcium-sensing receptors and proteins linked to the hormone parathyroid, leading to the design of cathepsin K and Src tyrosine kinase inhibitors, calcilytics, and monoclonal antibodies against sclerostin or Dickkopf-1 (**Table 2**).

Nanoenabled systems for the systemic delivery of drugs for the treatment of MBD have attracted huge attention in recent times. A number of formulations were

Class of drug	Investigational drug	Characteristics	Mode of action	Therapeutic efficacy	References
Calcilytics	MK-5442 (Phase II)	Orally bioavailable	CaSR antagonist	Transient PTH pulses and a dramatic rise in the formation of bone markers were noted, with a transitory significant decline in markers of bone resorption. Compared to placebo, no further rise in BMD was reported	[36]
Cathepsin K inhibitors	ODN	Long half-life, orally bioavailable	Inhibits CatK from binding to its corresponding substrates	Reduced bone turnover in ovariectomized animals and promoted periosteal bone formation was observed	[37]
	ONO-5334	Synthetic derivative, low molecular weight, oral formulation	Inhibits CatK from binding to its corresponding substrates	In Phase 2 clinical trial in postmenopausal women with osteoporosis, there was a substantial enhancement in BMD in the lumbar spine, total hip, and femoral neck compared to placebo. The observed effect on BMD of ONO-5334 was found to have a similar effect as that of alendronate, when administered at a dose of 70 mg once weekly	[38]
Src tyrosine kinase inhibitors	Saracatinib (AZD0530)	Oral formulation	Inhibits the enzyme Src kinase competitively	A notable decrease in bone resorption markers without any noticeable effect on bone formation markers and no serious adverse effects was documented, demonstrating a reduction in osteoclast bone resorption effect of saracatinib	[39]
Monoclonal antibodies against sclerostin/ Dickkopf-1	Romosozumab (AMG-785)	Human monoclonal anti-sclerostin antibody	Monoclonal antibody against sclerostin	A rise in dose-dependent BMD at the lumbar spine and total hip with a decrease in bone resorption markers with marked improvement in bone formation markers after a period of 3 months was reported	[40]

PTH, parathyroid hormone; CaSR, calcium sensing receptor; BMD, bone mineral density; CatK, cathepsin K.

Table 2.
Recent advances for the treatment of metabolic bone disease.

designed for the controlled delivery of medicaments for better therapeutic efficacy with minimal associated adverse effects. Some of the formulations reported in this specified category include tigecycline entrapped calcium phosphate/poly-DL-lactide-co-glycolide nanoparticles, titanium implants coated with bisphosphonate encased calcium phosphate nanoparticle, and gold nanoparticles incorporated gelatin-based hydrogel. Reports suggest that surface reconfiguration through nanotechnology has played a significant role in the design and manufacture of better spinal implants [41–44].

6. Conclusion

The burgeoning of the incidences of MBD is raising concern worldwide. Proper screening of the disorder is of prime importance in dealing with it. Although bisphosphonates remain the first-line treatment choice for the stated disorder, researchers should work upon the novel drugs with a unique mode of action and appreciable long-term safety profile. Based on the literature, it is pertinent to state that a fine balance between the non-pharmacological and pharmacological approaches could help out in dealing with MBD judiciously resulting in its prevention. Therefore, the battle for the search of better drugs for treating patients with metabolic bone diseases continues with an aim to provide better therapeutic efficacy and patient compliance.

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